immunization. Accordingly, the Panel recommended that those products containing a diphtheria or tetanus toxoid component for which there were inadequate clinical data be placed in Category I for booster use and Category IIIA for primary immunization. Since the Panel completed its review, additional clincial data applicable to both primary and booster immunization have been made available to FDA. These additional data are applicable to the clinical response elicited by several toxoid containing products. Data have been provided both for products which were licensed after 1972 and for some licensed products reviewed by the Panel. The products all met the existing animal potency requirements of FDA as well as other requirements for release. Not all clinical data completely meet the criteria of the sample protocol described by the Panel for assaying the efficacy of tetanus toxoid in humans, e.g., number of subjects, percent with titers greater than 0.01 units, or method used for antitoxin assay.

FDA has submitted additional clinical data for review by the Advisory Committee for the following products: Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, and Tetanus Toxoid Adsorbed, Connaught Laboratories, Inc., License No. 711; Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, Tetanus Toxoid Adsorbed, Lederle Laboratories, Division American Cyanamid Co., License No. 17; Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), (tetanus toxoid component only), Wyeth Laboratories, Inc., License No. 3.

FDA is not aware of additional serologic data applicable to the use of the following licensed products for primary immunization: Diphtheria and Tetanus Toxoids Adsorbed, and Tetanus Toxoid Adsorbed, Michigan Department of Public Health, License No. 99; Tetanus Toxoid, Istituto Sieroterapico Vaccinogeno Toscano Sclavo, License No. 238; Tetanus Toxoid Adsorbed, Swiss Serum and Vaccine Institute Berne, License No. 21; Diphtheria and Tetanus Toxoids Adsorbed, Tetanus Toxoid, Tetanus Toxoid Adsorbed, and the diphtheria component of Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Wyeth Laboratories, Inc., License No. 3.

FDA is not at this time judging the adequacy of the data cited above and is not proposing a regulatory classification for those products recommended for Category IIIA by the Panel. All data for these products are under review by the Advisory Committee and will be reclassified in either Category I or II. FDA will announce its evaluation of the data in a proposed rule after consideration of the Advisory Committee's recommendations.

e. *Category IIIB. Biological product for which available data are insufficient to classify its safety and effectiveness and should not continue in interstate commerce:* Gas Gangrene Polyvalent Antitoxin, Lederle Laboratories, Division American Cyanamid Co., License No. 17.

FDA agrees with the Panel's findings; however, because the license for Gas Gangrene Polyvalent Antitoxin was revoked at the manufacturer's request on March 12, 1981, no further FDA action is necessary.

f. *Category IIIC.* A Category "IIIC" designation is not defined in § 601.25, pursuant to which the review process for biological products is established. FDA appreciates that in establishing a Category "IIIC" the Panel wished to make explicit its opinion that certain of its recommendations for revocation of licenses were based on administrative and procedural problems and were not judgments derived from a scientific evaluation of the products. For example, some licenses are held for products which the manufacturer has not produced or marketed for many years. Other licenses are held for products for which there is no labeling, and which are manufactured only for combination with other biologically active components. As a result, the manufacturers submitted incomplete or outdated information and labeling, if any, for the Panel's review. The concerns of the Panel regarding these issues were properly transmitted to the agency. However, these issues can be resolved within the mechanisms already provided in § 601.25, and the use by FDA of new Category IIIC is unnecessary FDA finds that Category IIIB (biological products for which available data for a product are insufficient to classify their safety and effectiveness and should not continue in interstate commerce), is appropriate regardless of whether the data for a product are scientifically insufficient or insufficient due to administrative and procedural deficiencies. Accordingly, with the exception of several antitoxin and immune globulin products noted below, the agency agrees with the Panel's recommendation that licenses for these biological drugs should be revoked because the available data are insufficient to classify their safety and effectiveness. Accordingly, FDA proposes to classify the products listed below in Category IIIB. In accordance with §§ 601.5 and 601.25(f)(2), the agency intends to publish a notice of opportunity for hearing (NOH) to revoke the licenses for these biological drugs.

(1) *Licensed biological products for which available data are insufficient to classify their safety and effectiveness and which should not continue in interstate commerce and for which the insufficient data are due to essentially administrative and procedural problems rather than scientific factors:* Tetanus Immune Globulin (Human), Abbott Laboratories, License No. 43; Diphtheria Toxoid, Istituto Sieroterapico Vaccinogeno Toscano Sclavo, License No. 238; Diphtheria Antitoxin, Tetanus Antitoxin, Tetanus Toxoid, Massachusetts Public Health Biologic Laboratories, License No. 64; Cholera Vaccine, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, Typhoid Vaccine, Merck Sharp & Dohme, Division of Merck & Co., Inc., License No. 2; Diphtheria Antitoxin, Diphtheria Toxoid Adsorbed, Michigan Department of Public Health, License No. 99; Tetanus Antitoxin, Swiss Sérum and Vaccine Institute Berne, License No. 21; Diphtheria Toxoid, Diphtheria Toxoid Adsorbed, Pertussis Vaccine, Wyeth Laboratories, Inc., License No. 3.

(2) *Biological products also recommended for Category IIIC but for which the product licenses have been revoked at the manufacturer's request subsequent to the Panel's review:* Diphtheria Toxoid, Diphtheria Toxoid and Pertussis Vaccine Adsorbed, Pertussis Vaccine, Dow Chemical Co., License No. 110; Tetanus Immune Globulin (Human), E.R. Squibb & Sons, Inc., License No. 52; Botulism Antitoxin, Diphtheria Antitoxin, Pertussis Vaccine, Tetanus and Gas Gangrene Polyvalent Antitoxin, Tetanus Antitoxin, Lederle Laboratories, Division American Cyanamid Co., License No. 17; Diphtheria Toxoid, Massachusetts Public Health Biologics Laboratories, License No. 64; Diphtheria Toxoid, Pertussis Vaccine, Tetanus Antitoxin, Merrell-National Laboratories, Division of Richardson-Merrell, Inc., License No. 101; Tetanus Immune Globulin (Human), Metabolic Inc., License No. 415; Pertussis Vaccine, Michigan Department of Public Health, License No. 99; Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and

Poliomyelitis Vaccine, Diphtheria and Tetanus Toxoids and Pertussis and Poliomyelitis Vaccine Adsorbed, Diphtheria Toxoid, Diphtheria Toxoid Adsorbed, Pertussis Vaccine, Pertussis Vaccine Adsorbed, Tetanus Antitoxin, Parke-Davis, Division of Warner-Lambert Co., License No. 1.

Merrell-National Laboratories, Division of Richardson-Merrell, Inc., transferred its manufacturing processes and facilities for manufacturing Diphtheria Toxoid, and Pertussis Vaccine to Connaught Laboratories, Inc. Connaught was issued License No. 771 on January 3, 1978.

Abbott Laboratories transfered its manufacturing process and facilities for manufacturing Tetanus Immune Globulin (Human) to Alpha Therapeutic Corp. for whom License No. 744 was issued on August 15, 1978.

The possible revocation of the licenses for the individual vaccines listed above will not jeopardize the availability or license of combination products which contain the individual vaccine.

The regulation on permissible combinations, § 610.17 (21 CFR 610.17), requires that a manufacturer of a combination biological product be licenses for the combination product. In addition, to assure that the individual therapeutic, prophylactic, or diagnostic products in the combination products are compatible, safe, potent, and effective, it was previously the agency's policy to require the manufacturer of a combination product to obtain a license for each product in the combination. Although FDA has not enforced this policy for a number of years, some manufacturers continue to retain licenses for individual vaccines, even though the manufacturer does not intend to market the product in that form. In addition, some vaccines were initially prepared as monovalent products, but subsequently such products were no longer marketed. As announced for viral and rickettsial vaccines in the **Federal Register** of April 15, 1980 (45 FR 25652), FDA has revised its policy to permit the licensing of combination vaccines without requiring the licensure of the individual component vaccines, provided appropriate data are submitted showing the compatibility, safety, and effectiveness of the combination product. In the event a component vaccine is purchased from another licensee, the manufacturer of each purchased vaccine must be identified in the package insert for the combination product, in accordance with the requirements for divided manufacture (21 CFR 610.83). Thus, FDA may revoke the licenses for many of the individual vaccines or toxoids listed above without jeopardizing the availability or license of the combination products in which they are incorporated.

FDA disagrees with the Panel's recommendations concerning Diphtheria Antitoxin and Tetanus Antitoxin manufactured by Massachusetts Public Health Laboratories and Tetanus Antitoxin manufactured by Swiss Serum and Vaccine Institute Berne. The Panel recommended that each of these products be placed in Category IIIC because no information or labeling for the products was submitted by the manufacturers for the Panel's review. FDA proposes that the products be placed in Category I.

After the Panel had completed review of Diphtheria Antitoxin and Tetanus Antitoxin, FDA accepted amendments from Massachusetts Public Health Laboratories and Swiss Serum and Vaccine Institute Berne to update the licenses for their antitoxin products to reflect current good manufacturing practices. No clincial data concerning the effectiveness of the products were submitted with the amendments; however, limited clinical data are available in support of the safety and effectiveness of Tetanus Antitoxin manufactured by Massachusetts Public Health Laboratories. FDA concurs with the Panel's finding that there is a sufficient body of evidence suggesting that Diphtheria Antitoxin and Tetanus Antitoxin are of some effect, albeit marginal, in the prophylaxis and treatment of diphtheria and tetanus, respectively. The available data do not demonstrate unequivocally the effectiveness of any licensed Diphtheria or Tetanus Antitoxin. However, FDA recognizes the difficulties in constructing controlled clinical studies to prove the effectiveness of these antitoxins for the prevention and treatment of these rare, life-threatening diseases. Accordingly, FDA finds that the existing clinical evidence, as corroborated by the long history of diphtheria and tetanus antitoxins' successful use, are adequate to find Diphtheria Antitoxin and Tetanus Antitoxin manufactured by Massachusetts Public Health Laboratories and Tetanus Antitoxin manufactured by Swiss Serum and Vaccine Institute Berne safe and effective for their intended uses.

FDA disagrees with the Panel's recommendation that the product license for Tetanus Immune Globulin (Human) (TIG), formerly manufactured by Abbott Laboratories and now by Alpha Therapeutic Corp., be revoked. As noted by the Panel, this product is manufactured only as a partially processed material (dry globulin powder) and is intended only for export into foreign commerce for further manufacture. The agency does not object to this practice. Several other manufacturers of plasma derivatives are engaged in similar activities. Consistent with the agency's policy on such matters, the product license has been suitably amended to provide for the export of the partially manufactured product and complete export labeling has been approved. The manufacturer is also retaining on file a written agreement with each consignee for the product which includes the specifications required for further processing, labeling, or repackaging of the final product. The agency advises that, if Alpha Therapeutic Corp. should decide to manufacture TIG as a final product for sale in the United States, suitable labeling to accompany the final product must be approved by the agency and the manufacturer must demonstrate the ability to manufacture a safe and effective final product in conformance with the standards set in the regulations before the agency would permit the release of the final product for sale in the United States. Accordingly, FDA is proposing that Tetanus Immune Globulin (Human) manufactured by Alpha Therapeutic Corp. be classified in Category I as safe and effective.

B. General Recommendations

In the following paragraphs, FDA is responding to the Panel's general recommendations regarding the products under review and to the procedures involved in their manufacture and regulation.

2. The Panel recommended changes in the labeling of the biological products under review. The Panel also recommended a generic order and wording for information in the labeling of bacterial vaccines.

FDA agrees with the labeling changes recommended by the Panel. The labeling recommendations applicable to a group of products, rather than an individual licensed product, are summarized in paragraphs 13, 19, and 24 of this response. Those labeling recommendations concerning product use will be discussed with the Public Health Service's Immunization Practices Advisory Committee (formerly known as the Advisory Committee on Immunization Practices and still identified as ACIP). In the preamble to the final rule, FDA intends to advise the licensed manufacturers of products generically reviewed in this report, including products licensed after July 1, 1972, to submit appropriately revised

draft labeling to the Center for Drugs and Biologics (CDB), FDA for review and approval according to the schedule given at the end of this paragraph. FDA proposes that such draft labeling shall conform with the Panel's recommendations, as modified as a result of public comment and FDA's evaluation of the Report. FDA finds the Panel's recommended labeling content and format consistent with the current regulations and recommends that it be used as a general guideline for the revision of bacterial vaccine and toxoid labeling. FDA notes that two additional sections not mentioned by the Panel, entitled *Animal Pharmacology* and/or *Animal Toxicology* and *Clinical Studies*, may be included in product labeling.

The draft labeling shall also be consistent with the regulations governing the content and format for labeling of human prescription drugs (21 CFR 201.56 and 201.57). The effective dates for implementation of the labeling content and format regulations are codified under § 201.59 (21 CFR 201.59). Consistent with § 201.59, FDA proposes that draft labeling, revised in conformance with this report and with the content and format regulations, should be submitted for FDA review no later than 6 months after the date of publication of the final rule based on this proposal. FDA is also proposing to require that such revised labeling accompany all products initially introduced or initially delivered for introduction into interstate commerce no later than 30 months after the date of publication of the final rule.

3. The Panel noted a number of labeling deficiencies (discussed in detail in the Panel's review of products) and expressed its belief that substantial improvement should be made in the labeling for biological products. To implement these improvements, the Panel recommended that labeling be reviewed and revised as necessary at intervals of no more than every 2 years.

FDA agrees that labeling for biological products should be improved; however, FDA believes the current system of labeling review will adequately assure accurate labeling. One of the important objectives of each advisory panel's review of biological products is to ensure that the labeling for the products under review is revised and updated according to the most recent scientific knowledge. As described elsewhere in this response, many products have not been manufactured for many years and, as a result, may have outdated labeling. The licenses for these products are either being proposed for revocation or have already been revoked; the labeling for the remaining products will be revised consistent with the Panel's recommendations and the current regulations.

It is the agency's policy to request that labeling be revised as indicated by current scientific knowledge and when the recommendations for the use of a given product have been significantly revised by ACIP or another responsible public organization. Revised draft labeling is then submitted by the manufacturer(s) for review and approval by FDA. FDA's Office of Biologics Research and Review also monitors the revision dates for the labeling for each licensed biological product. If a significant period of time has elapsed since the last labeling revision and it appears that the labeling may be outdated, the manufacturer of the product is asked to inform the agency of the status of the product, including its labeling. From the manufacturer's response, the agency can determine whether revision of the labeling may be appropriate.

In some cases, labeling must be revised as a result of changes in the regulations. In such circumstances, the agency sets an effective date by which time labeling revised in accordance with the regulations must accompany the product. In instances where, for routine updating purposes, the manufacturer has submitted updated draft labeling for agency approval, the manufacturer is asked to notify the agency when the new labeling is put into use. If the labeling revision would significantly affect a product's use, the Office of Biologics Research and Review may request at the time of approval of the draft labeling that the new labeling be put into use by a specified date. Otherwise, FDA requests the manufacturer to notify the agency of the date the new labeling is put into use, to provide the identifying number of the product the approved labeling first accompanied, and to submit a copy of the approved final labeling for the agency's files. Thus, the agency is able to monitor continually the labeling in use for each licensed product, assuring that the labeling is consistent with current scientific knowledge and regulations. Accordingly, FDA believes it is unnecessary to specify a time interval, such as every 2 years, for the review and revision of labeling for biological products.

4. The Panel recommended that actions be taken to improve the reporting and documentation of adverse reactions to biological products. The Panel particularly noted the need to improve the surveillance systems to identify adverse reactions to pertussis vaccine.

Manufacturers voluntarily submit individual and/or periodic summaries of the reaction reports they have received to CDB. FDA receives reports from consumers both directly and through the United States Pharmacopeia (U.S.P.) Problem Reporting Program, the Drug Experience Reporting System, and the Government-Wide Quality Assurance Program. All of these reaction reports for biologics are reviewed at CDB, entered in a computer data base, and appropriate action taken. FDA investigators also routinely review complaint files maintained by biological product manufacturers.

The Centers for Disease Control (CDC) maintain another product surveillance system and receive adverse reaction reports primarily from local and State health departments. FDA and CDC frequently exchange information regarding reactions to biological products.

FDA recently supported a study to determine the incidence of reactions associated with DTP and DT immunization (Ref. 1). This study provided information similar to other reports since 1978 (Refs. 2 and 3).

A case-control study of neurological damage attributable to pertussis vaccine has been completed in the United Kingdom (National Encephalopathy Study). These data provide information which may be applicable to estimating the predicted incidence of local and systemic reactions to pertussis vaccine, including the incidence of severe neurological disorders.

The agency's systems for reporting of adverse reactions are continually under review by FDA. However, FDA believes that a discussion of FDA's systems for reporting and processing of adverse reactions to biological products is outside the scope of this rulemaking.

5. The Panel recommended that all licensed vaccines be periodically reviewed to assure that the data concerning the safety and effectiveness of these products are kept current and that the licenses be revoked for products which have not been marketed for years or which have never been marketed in the licensed form. The Panel noted that some standards of purity, immunogenicity, and immune responses for older well-established vaccines are based upon methods that should be updated by more sophisticated techniques made possible by advancing scientific knowledge. The Panel noted that by limiting the period for which specific vaccines may be licensed, older products would be assured periodic

review and new products for which additional efficacy data are required could be provisionally licensed for only a limited period of time within which additional data can be generated.

The agency believes it would be unnecessary and burdensome to review comprehensively at defined intervals the data held in the license applications for each biological product. It is the continuing agency policy to require product standards consistent with current biomedical knowledge and technology and to revise such standards whenever sound and substantiated laboratory and clinical data demonstrate that changes in methods of production and testing would result in a better product. Under § 601.12(a) (21 CFR 601.12(a)), licensees are required to report any important changes in manufacturing procedures to FDA. Some important changes in manufacturing processes may require submission of additional supporting clinical data prior to the agency's approval. Through these means, the agency believes that the data, standards, and manufacturing process for actively manufactured biological products are kept consistent with current biomedical knowledge.

The majority of the instances where data or manufacturing processes appeared outdated to the Panel were for products that have not been marketed in many years or were never marketed in the licensed form. The licenses for these products are proposed for revocation as part of the implementation of this efficacy review.

The Panel's recommendation that some new vaccines be provisionally licensed for only limited periods of time while additional required data on effectiveness are generated cannot be implemented under present law which requires that a biological product be determined to be safe, pure, and potent before it is licensed.

6. The Panel recommended that compensation from public funds be provided to individuals suffering injury from vaccinations that were recommended by competent authorities, carried out with vaccines which passed official safety and efficacy requirements, and when the injury was not a consequence of defective or inappropriate manufacture or administration of the vaccine.

A similar recommendation concerning a public compensation system was made at the National Immunization Conference held in April 1977. Such a public compensation system has been under study by the Department of Health and Human Services. The Department has testified before the Senate and House during the 98th Session of Congress regarding two bills (S. 2117 and H.R. 5810), which would establish a Federal vaccine compensation program. Both bills have laudable goals and reflect many of the recommendations that have been made to the Department over the past several years by different groups. These bills, however, also have major weaknesses which made them impossible for the Department to support and which interrelate to provide a significant disincentive to vaccine programs.

The vaccine compensation issue is a very complicated area and one in which there may be no single simple solution. The Department is analyzing the position of the American Medical Association and the American College of Physicians and will soon review the report of the Institute of Medicine. A thorough analysis of these proposals is important to the development of a position on this complex issue of compensation.

7. The Panel recommended that both FDA and the public support widespread immunization programs for tetanus, diphtheria, and pertussis.

FDA agrees that the immunization of children for tetanus, diphtheria, and pertussis should continue to be emphasized. Such immunization programs are part of national policy. In April 1977, the Department announced a plan to achieve immunization of the 3 million infants born in the United States each year as well as those already born who had not been immunized. The target diseases included tetanus, diphtheria, pertussis (under age 7), measles, mumps (under age 7), rubella, and polio. The national program successfully raised immunization levels from a range of 66 to 75 percent in 1977 to immunization levels of 95 percent or greater for these diseases in children entering school for the school year 1981–1982. The Department has affirmed that the immunization program will continue to be emphasized (Ref. 4).

8. The Panel recommended that the agency work closely with the CDC and other appropriate groups to ensure that adequate supplies of vaccines and passive immunization products continue to be available. The Panel was especially concerned about products that are available solely from foreign firms; products for which there is only a single domestic manufacturer; and products for which discontinuation of production is possible or probable for commercial reasons, despite current or potential needs. The Panel recommended establishment of a national vaccine commission to address such issues.

FDA agrees that the government should cooperate with industry, the health professions, and the public to ensure adequate production and supply of vaccines and other immunization products. The agency believes that the establishment of such a commission is unnecessary because the government is already extensively involved in production and supply issues through such efforts as the National Institutes of Health [NIH] research program, FDA's release of products shown to be safe and effective, and CDC's epidemiological/surveillance programs which help to predict future needs. These agencies now cooperate extensively.

9. The Panel recommended that the protocols for efficacy studies should be reasonably consistent throughout the industry for any generic product. To achieve this goal, the Panel recommended the development of industry guidelines that provide standardized methodology for adducing required information.

The agency believes that the development of general guidelines for conducting studies on vaccine products is not practical at this time. Most study protocols are uniquely designed to meet the individual objectives of each clinical study and to accommodate the characteristics of the vaccine and the size and qualifications of the test population available for the study. In addition, it is rare that a significant number of manufacturers will initiate clinical studies on similar biological products within a reasonably short period of time; the situation where guidelines would be most useful. Accordingly, the agency intends to continue its policy of cooperating with manufacturers on an ad hoc basis in discussing possible clinical studies and to comment on proposed protocols for studies to demonstrate clinical potency (efficacy) and safety of vaccine products. FDA scientists generally review and comment upon protocols for FDA required clinical studies on vaccines before studies are initiated. FDA believes that the current system allows the manufacturer maximum flexibility in selecting the appropriate tests and procedures for a clinical study while assuring that the necessary data are generated to fulfill the intended objectives of the study.

10. The Panel expressed concern that regulations governing informed consent and the protection of human subjects involved in clinical investigations should not establish unnecessary impediments to the equally worthwhile goal of obtaining adequate evidence for

the safety and effectiveness of a product.

FDA believes that the Panel's concerns are unwarranted. FDA does not believe that the regulations governing informed consent and the protection of human subjects involved in research activities (21 CFR Parts 50 and 56) impose unnecessary impediments to obtaining adequate evidence for the safety and effectiveness of the products under the agency's jurisdiction. The Panel's report was prepared before the publication of the proposed and final rules clarifying the requirements governing informed consent and the protection of human subjects. The final rule concerning these matters (46 FR 8942; January 27, 1981) requires the informed consent of all human subjects, or their legal guardian, involved in research activities under FDA's jurisdiction. The regulations also require that the research activities be reviewed and approved by an institutional review board (IRB) to assure the adequate protection of the human research subjects. FDA is unaware, through public comment or the agency's own investigations, of these requirements having hindered the gathering of a suitable subject population for a research activity.

C. Response to Recommendations Concerning Specific Products

In the following paragraphs, FDA is responding to those Panel recommendations relating to specific licensed products.

11. The Panel recommended that FDA encourage further studies on the use of adjuvants in bacterial vaccines and toxoids.

FDA agrees that further investigation is appropriate on the use of adjuvants in biological products. Since the Panel completed its review, further data from the Connecticut Tumor Registry show that no changes in the incidence of soft tissue sarcomas of the upper arm were observed which could be attributed to the use of alum (Ref. 5). These data were directly related to introduction of alum adsorbed allergens but are also relevant to the use of aluminum adjuvants in topical vaccines. FDA continues to monitor information regarding the use of adjuvants in all types of products. In collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), and NIH, the Bureau of Biologics (now the Office of Biologics Research and Review, CDB) sponsored an International Symposium on Adjuvants on February 20 to 21, 1979 (Ref. 6).

12. The Panel recommended that standards should be established for purity of both diphtheria and tetanus toxoids in terms of Limit of flocculation (Lf) content per milligram (mg) of nitrogen.

FDA agrees with the recommendation. The agency is currently developing information needed to propose additional standards for these two bacterial products, which would include proposed minimum purity requirements expressed in Lf content per milligram of nitrogen. The agency notes that the requirements of the World Health Organization (WHO) provide a minimum purity requirement of 1000 Lf/mg nitrogen for Tetanus Toxoid and 1500 Lf/mg nitrogen for Diphtheria Toxoid (Ref. 7). FDA invites comment on appropriate purity requirements for Tetanus and Diphtheria Toxoids licensed in the United States.

13 The Panel recommended that the immunogenic superiority of the adsorbed diphtheria and tetanus toxoids over the fluid (plain) preparations be strongly emphasized in product labeling, especially with regard to the duration of protection.

FDA agrees with the recommendation. The apparent immunogenic superiority of adsorbed toxoid over plain toxoid should be emphasized in product labeling. FDA notes that most toxoid products are already labeled consistent with this recommendation. FDA intends to require that the remaining applicable labeling be appropriately revised according to the schedule announced elsewhere in this proposal. The comparative immunogenic superiority of the adsorbed toxoids over the fluid toxoids was emphasized by ACIP in its most recent guidelines for vaccine prophylaxis of diphtheria, tetanus, and pertussis (Ref. 8).

14. The Panel noted a need for further studies with tetanus toxoids on a WHO sponsored quantitative potency test in animals to establish the conditions under which the test results are reproducible, and to relate these results more closely to those obtained in immunization of humans. The Panel also recommended the development of an animal or laboratory testing system for diphtheria toxoid that correlates consistently, and with acceptable precision, with primary immunogenicity in humans.

FDA agrees with the recommendations. For several years, FDA has participated in collaborative studies with WHO to evaluate international standards in terms of International Units per milliliter (IU/mL) for toxoids in animals. For tetanus toxoid, FDA has participated in collaborative studies with WHO to apply a quantitative potency test in both mice and guinea pigs (Refs. 9 and 10) and has compared the response to toxoids in women to that of guinea pigs and mice (Ref. 11). The Office of Biologics Research and Review, CDB, has assayed the IU/mL of many toxoids in both animal species in efforts to establish reference toxoids suitable for routine lot control. In addition, the potency (IU/mL) of many types of licensed tetanus toxoids has been assayed. CDB staff has recently completed a study in monkeys in which the relationship of the antitoxin response and the potency of several of these toxoids, as expressed in IU/mL, was examined. Some of these data have been published. (Ref. 12).

Only a few studies in man are available that utilized diphtheria toxoids with potencies defined in IU/mL by this procedure. As described below, FDA intends to continue to evaluate this procedure and is taking steps to provide suitable reference standards.

The Panel indicated that the potency tests now required for diphtheria and tetanus toxoids are suitable for determining the acceptability of the toxoids for booster use, but not for primary immunization. The agency is aware that the Panel was provided with a limited amount of data from studies of primary immunization. Both monovalent and combined products containing these toxoids, which passed the current potency tests for adsorbed toxoids, have been shown by manufacturers to induce adequate antitoxin responses when used as recommended for primary immunization. The products meeting the current potency tests yield satisfactory booster responses. Thus, FDA considers the current animal potency assays suitable for routine potency determinations. The agency agrees that limited data support the use of the current potency tests for evaluating the fluid toxoids for use in primary immunization. However, the limited available data do support the efficacy of fluid tetanus toxoid. No Diphtheria Toxoid fluid is currently being marketed.

In addition to meeting the current potency requirements, the agency recommends that the potency of toxoids administered in future clinical studies be assayed for IU/mL using appropriate protocols and references. In this manner, the response in humans could be compared to that of guinea pigs and/or mice, so that eventually the correlation between laboratory data and clinical effectiveness can be firmly established. In evaluating such studies, host responses may require evaluation as well, e.g., effect of age, sex, or